

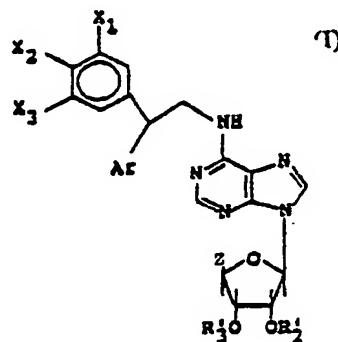
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

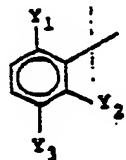
74

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

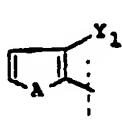
(51) International Patent Classification ⁴ :	A1	(11) International Publication Number: WO 88/03147
C07H 19/167, A61K 31/70		(43) International Publication Date: 5 May 1988 (05.05.88)
(21) International Application Number: PCT/US87/02719		44833 Tillotson Drive, Canton, MI 48187 (US).
(22) International Filing Date: 19 October 1987 (19.10.87)		(74) Agents: THIERSTEIN, Joan; 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.
(31) Priority Application Numbers: 925,185 090,830		(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US, US.
(32) Priority Dates: 31 October 1986 (31.10.86) 28 August 1987 (28.08.87)		
(33) Priority Country: US		
(60) Parent Applications or Grants		
(63) Related by Continuation		
US Filed on 31 October 1986 (31.10.86)	925,185 (CIP)	
US Filed on 28 August 1987 (28.08.87)	090,830 (CIP)	
(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).		
(72) Inventors; and		
(75) Inventors/Applicants (for US only) : BRIDGES, Alexander, James [GB/US]; 2175 Steeplechase, Ann Arbor, MI 48103 (US). ORTWINE, Daniel, Fred [US/US]; 663 Springbrook Court, Saline, MI 48176 (US). TRIVEDI, Bharat, Kalidas [IN/US];		

(54) Title: SELECTED N⁶-SUBSTITUTED ADENOSINES HAVING SELECTIVE A₂ BINDING ACTIVITY

(II)



(III)



(IV)



(57) Abstract

Adenosines of formula (I), wherein Ar is (II), (III) or (IV), wherein A is oxygen or sulfur. The adenosines have highly selective A₂ receptor binding activity and useful properties advantageous in treating cardiovascular diseases, such as hypertension, angina or myocardial ischemia, pain, insomnia and psychosis. Also a novel preparation of selected adenosines.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT Austria	FR France	ML Mali
AU Australia	GA Gabon	MR Mauritania
BB Barbados	GB United Kingdom	MW Malawi
BE Belgium	HU Hungary	NL Netherlands
BG Bulgaria	IT Italy	NO Norway
BJ Benin	JP Japan	RO Romania
BR Brazil	KP Democratic People's Republic of Korea	SD Sudan
CF Central African Republic	KR Republic of Korea	SE Sweden
CG Congo	LJ Liechtenstein	SN Senegal
CH Switzerland	LK Sri Lanka	SU Soviet Union
CM Cameroon	LU Luxembourg	TD Chad
DE Germany, Federal Republic of	MC Monaco	TG Togo
DK Denmark	MG Madagascar	US United States of America
FI Finland		

-1-

SELECTED N⁶-SUBSTITUTED ADENOSINES HAVING SELECTIVE A₂ BINDING ACTIVITY

This is a continuation-in-part of US Application Serial Number 925,185 filed October 31, 1986.

BACKGROUND OF THE INVENTION

The compounds of the present invention are related to the N⁶-substituted adenosines of copending application U.S. Serial Number 756,922 filed June 17, 1985 which is a continuation of U.S. Serial Number 621,943 filed June 22, 1984 now abandoned, which is a continuation in part of U.S. Serial Number 519,284, filed August 1, 1983 now abandoned.

The instant compounds have a surprisingly greater affinity for A₂ receptors than A₁ receptors. The compounds have highly desirable central nervous system and cardiovascular activities, such as analgesic, antipsychotic, sedative, antihypertensive, and cardiotonic activity, especially, antianginal and vasodilator effects.

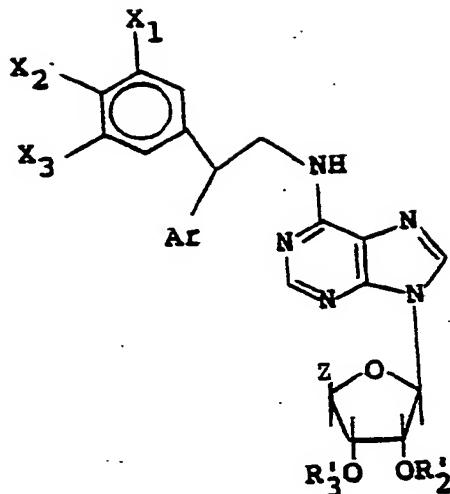
Thus, the above noted copending application and references therein provide a background for the present invention including descriptions of literature assays in which the compounds of the present invention have been found to possess activity as described herein. Therefore, copending application U.S. Serial Number 756,922 is incorporated by reference.

References related to the novel process of the present invention include European Application 222330A, J. Med. Chem., Vol. 29, No. 9, pp. 1683-89 (1986) or WO8600310, and J. Med. Chem., Vol. 23, pp. 313-9 (1986) or U.S. Patent No. 3,852,268. None of these references show the preparation of a 5' uronamide from inosine isopropylidene of the present novel process having unexpected advantages.

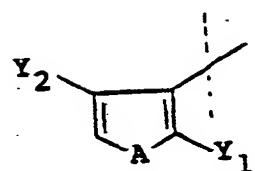
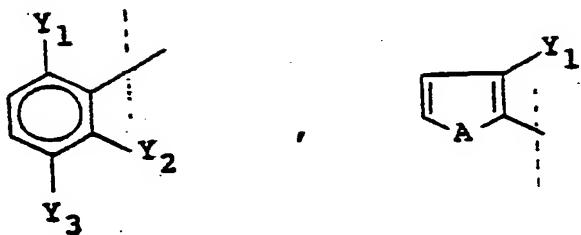
SUMMARY OF THE INVENTION

The present invention relates to a compound of the formula (I)

-2-



or a pharmaceutically acceptable acid addition salt thereof;
wherein Ar is



wherein X₁, X₂, X₃, Y₁, Y₂ and Y₃ may be independently selected from hydrogen, halogen, lower alkyl, lower alkylthio or alkoxy, and X₁, X₂, X₃ may also be trifluoromethyl with the proviso that Y₂ or Y₃ must be hydrogen except when Y₁ is hydrogen and

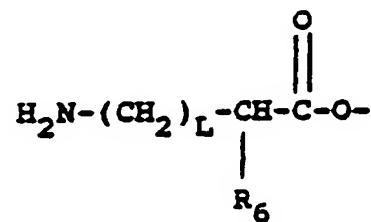
10

-3-

Y_2 and Y_3 taken together are $-(CH)_4$ with the further overall proviso that at least two of X_1 , X_2 , X_3 , Y_1 , Y_2 and Y_3 are not hydrogen.

5 R_2' and R_3' are each independently hydrogen, alkanoyl having two to twelve carbon atoms in a straight or branched alkyl chain which may be substituted by amino, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; additionally, R_2' and R_3' may be linked together to form either a five-membered alkylidene ring having 10 a total of up to twenty carbons such as, for example, isopropylidene, or a cyclic phosphate diester and R_5' may be a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium salt thereof, such as, for example, PO_3Na_2 ;

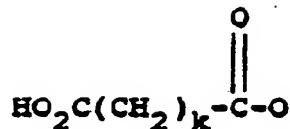
15 Z is $-(CH_2)_n-Q$ wherein Q is selected from the group consisting of hydrogen; hydroxy; halogen; cyano; azido; amino; lower alkoxy; lower acyloxy; lower thioalkyl; lower sulfonylalkyl;



20 wherein L is 0-4; and

R_6 is hydrogen or when L is 0 then R_6 may also be a side chain of a naturally occurring amino acid, such as, benzyl as found in a phenylalanine ester, or isopropyl as found in a valinyl ester or

-4-



wherein k is 0-4;

$-\text{P}(=\text{Y})(\text{OR}'')_2$, $-\text{P}(=\text{Y})(\text{OR}'')(\text{OR}''')$ and taken together with R^3 is

5



wherein Y is oxygen or sulfur and R'' and R''' are independently hydrogen or lower alkyl; or (2)



wherein J is O, S, NR₇ wherein R₇ is hydrogen, lower alkyl or cycloalkyl of from 3 to 7 carbons such as cyclopropyl, cyclobutyl, cyclopentyl and the like or 1- or 2-methylcyclopropyl, 1-, or 2-ethylcyclobutyl and the like; and

T is (a) NR₄R₅ wherein R₄ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the

-5-

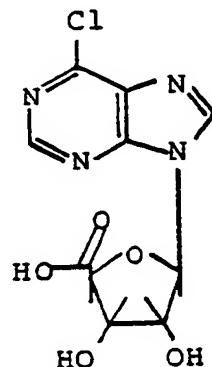
heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

R₅ is hydrogen or straight chain lower alkyl having 1 to 4 carbons; or

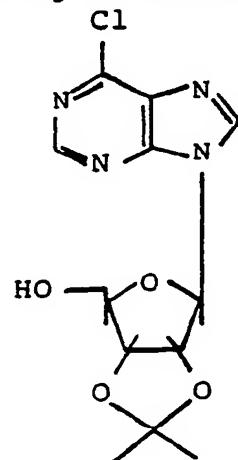
5 (b) OR₄ wherein R₄ is as defined above.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the above formula I with a pharmaceutically acceptable carrier, and to a method of treating mammals by administering to such mammals a dosage form of a compound of 10 the formula I as defined above.

Finally, the present invention is a novel process for preparing a compound of the formula



15 which comprises treating a compound of the formula



with H₂CrO₄ in acetone.

In the compounds of the formula I, the term "lower alkyl" is meant to include a straight or branched alkyl group having

-6-

from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amyl, isoamyl, neopentyl, hexyl, and the like.

Halogen includes particularly chlorine or bromine.

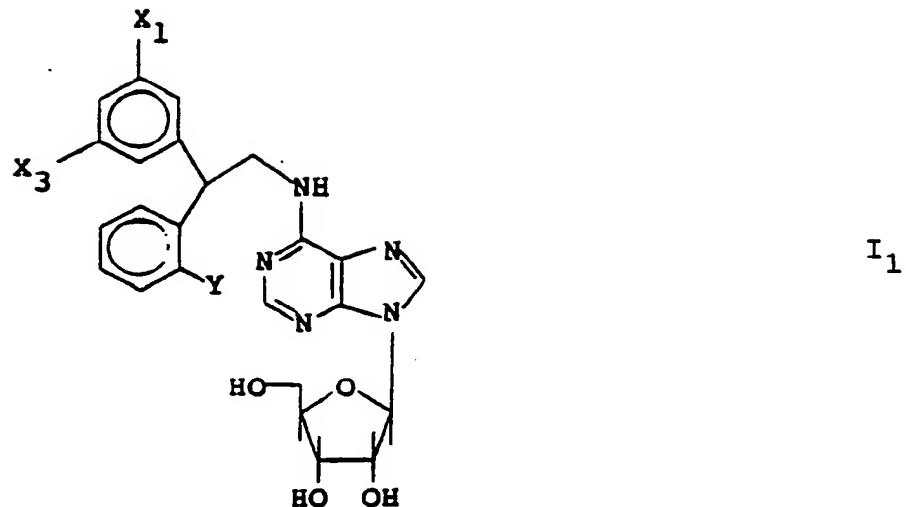
Lower alkoxy and thioalkoxy are O-alkyl or S-alkyl of from 5 1 to 6 carbon atoms as defined above for "lower alkyl".

The compounds of formula I are useful both in the free base form and in the form of acid addition salts. Both forms are within the scope of the invention. In practice, use of the 10 salt form amounts to use of the base form. Appropriate pharmaceutically acceptable salts within the scope of the invention are those derived from mineral acids such as hydrochloric acid and sulfuric acid; and organic acids such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic 15 acid, and the like, giving the hydrochloride, sulfamate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like, respectively. (See for example, "Pharmaceutical Salts", J. Pharm. Sci. (1977) 66(1):1-19.)

The acid addition salts of said basic compounds are 20 prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be 25 obtained by concentration of the solution.

Preferred compounds of formula I are

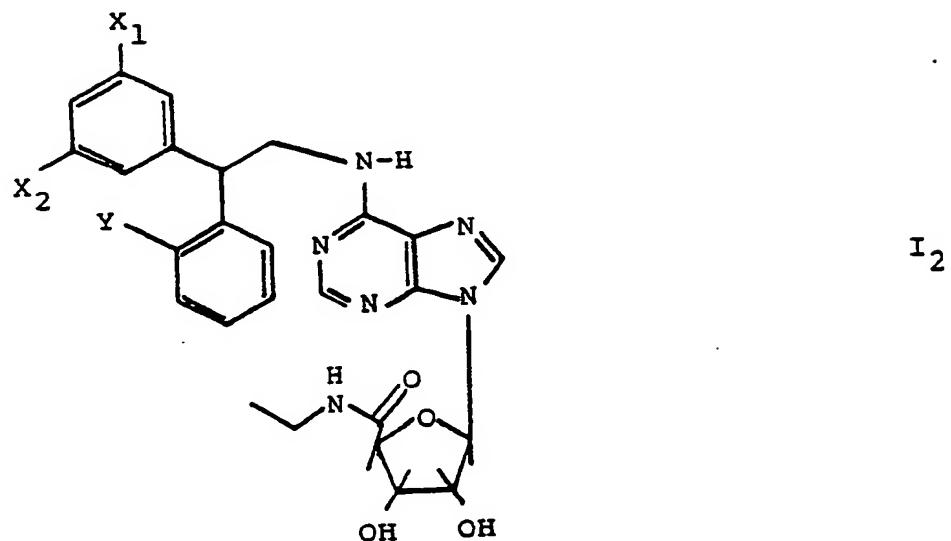
-7-



wherein X₁ and X₃ are as defined above and Y is Y₁ when Y₁ is not hydrogen.

Another group of preferred compounds of formula I is

5



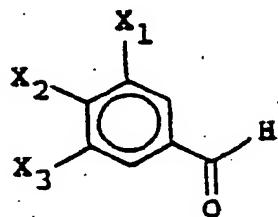
wherein X₁, X₂ and Y are as defined above.

The most preferred compound of the present invention is of the formula I₁ wherein X₁ and X₃ are methoxy and Y is methyl.

The present invention is also novel processes for the preparation of a compound of formula I as follows:

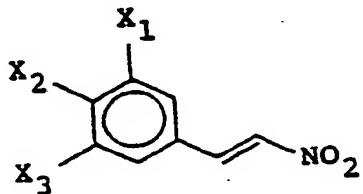
-8-

Generally, the compounds of formula I may be synthesized by conversion of an aryl aldehyde of formula (V)



V

wherein X_1 , X_2 and X_3 are as defined above; to the
5 corresponding w-nitrostyrene of the formula (IV)

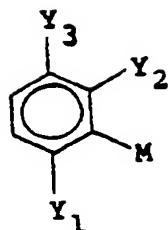


IV

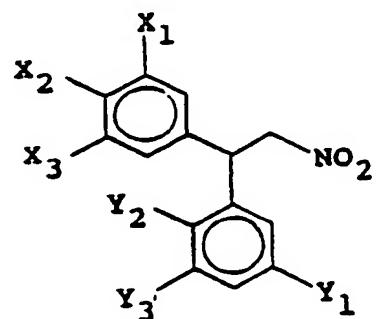
wherein X_1 , X_2 and X_3 are as defined above. The conversion is accomplished by (1) treating with nitromethane in basic medium, i.e. in a solvent such as methanol, ethanol, or aqueous 10 methenyl in the presence of NaOH, and (2) chlorosulfonylmethane in the presence of about two equivalents of triethylamine in an aprotic solvent such as dichloromethane.

The w-nitrostyrene of the formula IV is then treated with an organometallic compound of the formula IVa

-9-

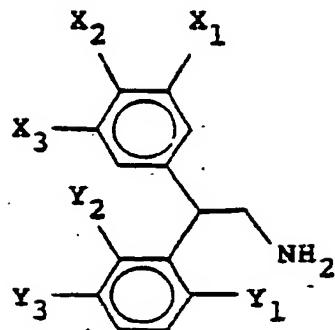


wherein Y_1 , Y_2 , and Y_3 are as defined above and M is a moiety preferably such that IVa is a Grignard or lithium derivative in an aprotic solvent system (preferably toluene-ether) at a low temperature (preferably from -10° to -40°C) using reaction conditions known by an ordinarily skilled artisan to be required by the Grignard or lithium derivative. Treatment with the organometallic compound gives a compound of formula (III)



wherein X_1 , X_2 , X_3 , Y_1 , Y_2 , and Y_3 are as defined above. The compound of formula III is then reduced by treatment with, for example, lithium aluminum hydride using conditions within the skill of an ordinarily skilled artisan to give a compound of the formula (II)

-10-



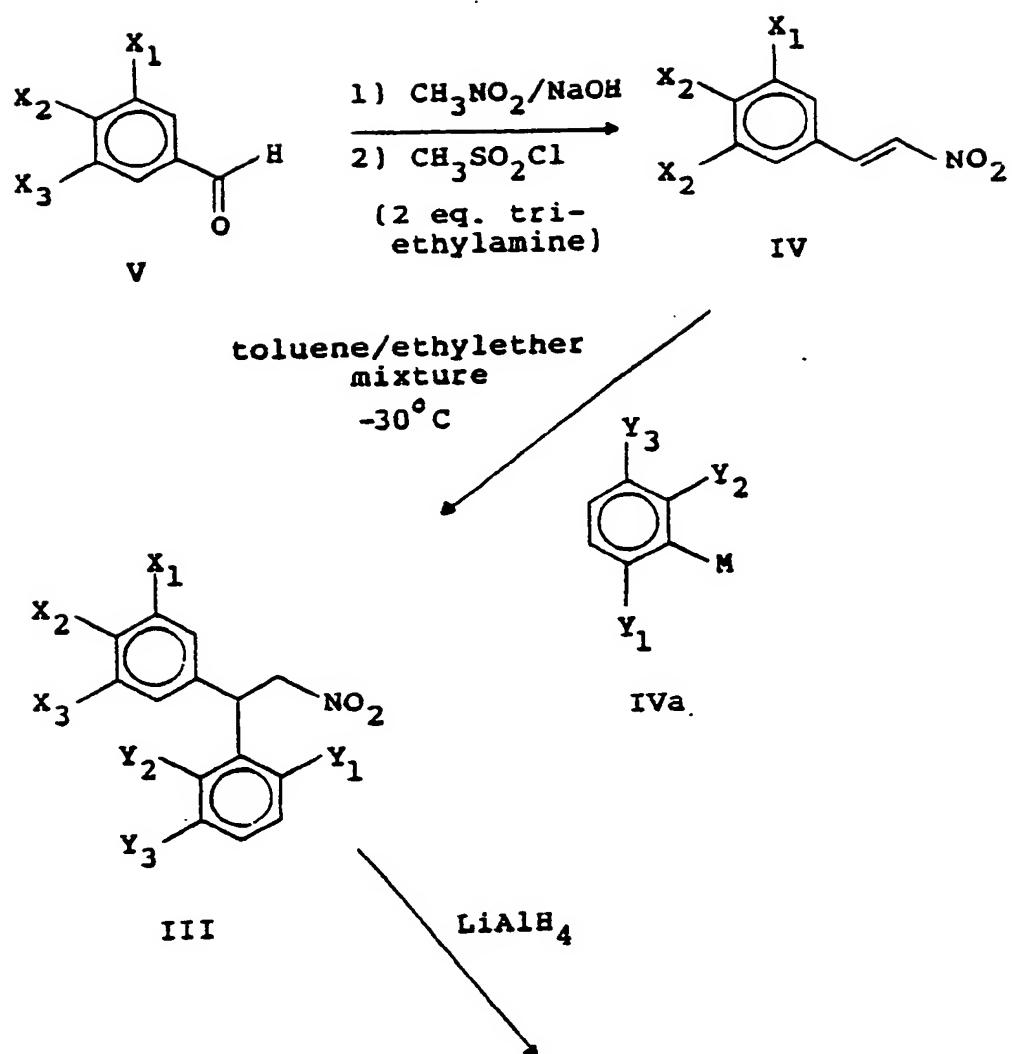
II

wherein X_1 , X_2 , X_3 , Y_1 , Y_2 and Y_3 are as defined above.

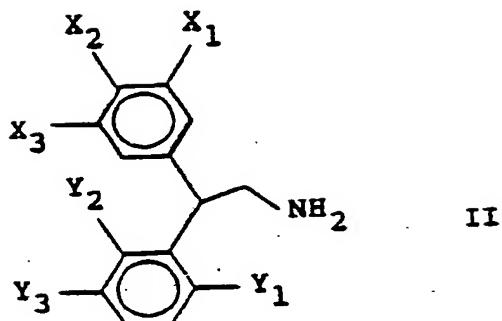
Finally, the compound of formula II is coupled with 6-chloropurine riboside in the presence of triethylamine according to the procedure as described in application U.S. Serial Number 756,922 to obtain a compound of formula I as defined above.

5

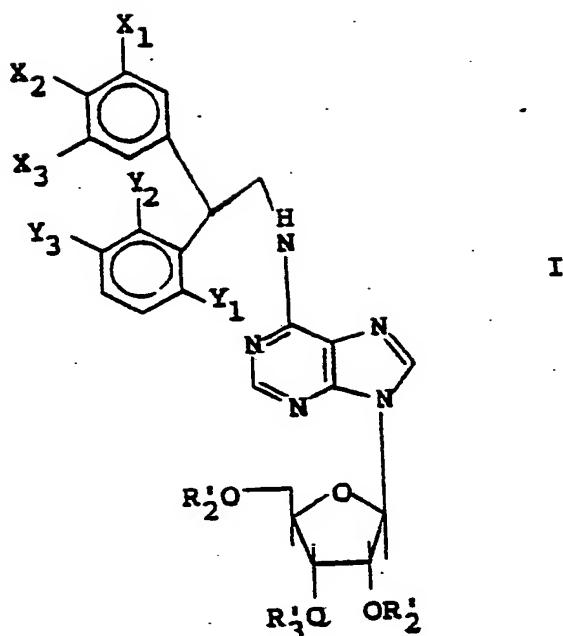
The above described process can be shown as follows:



-12-

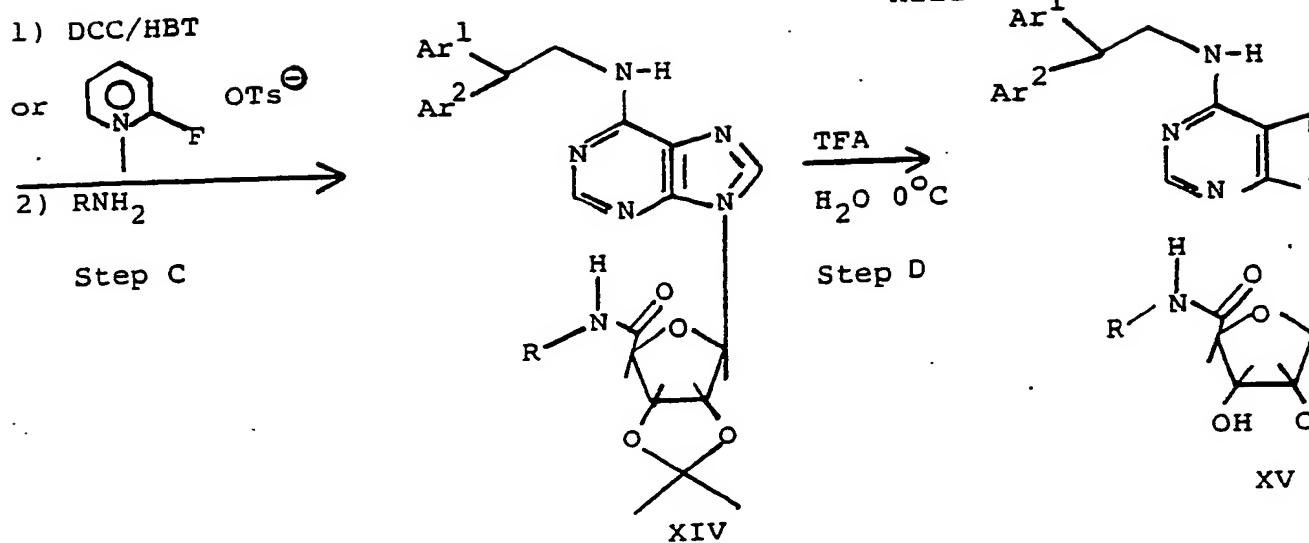
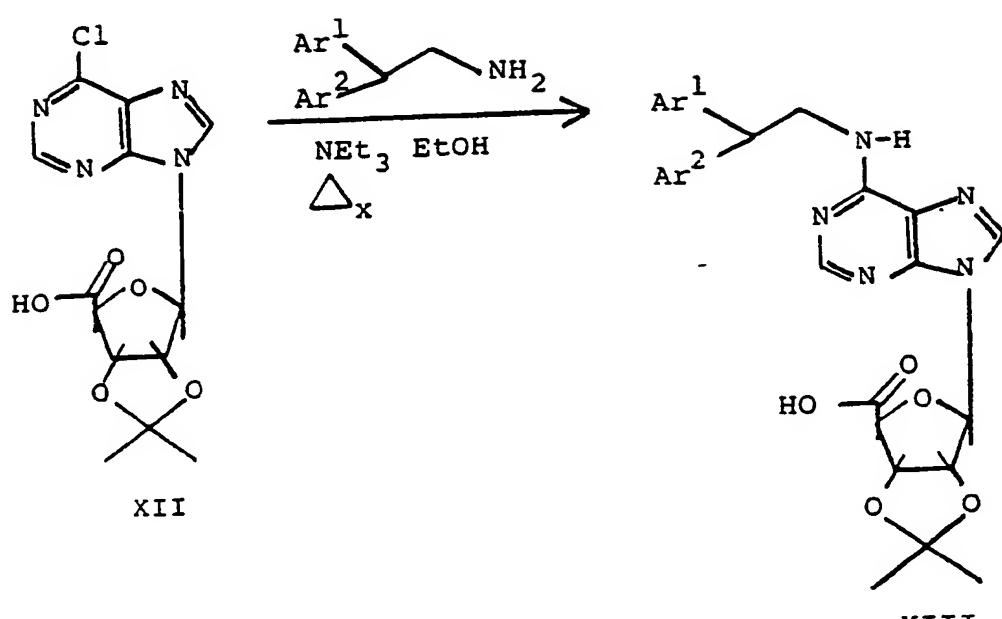
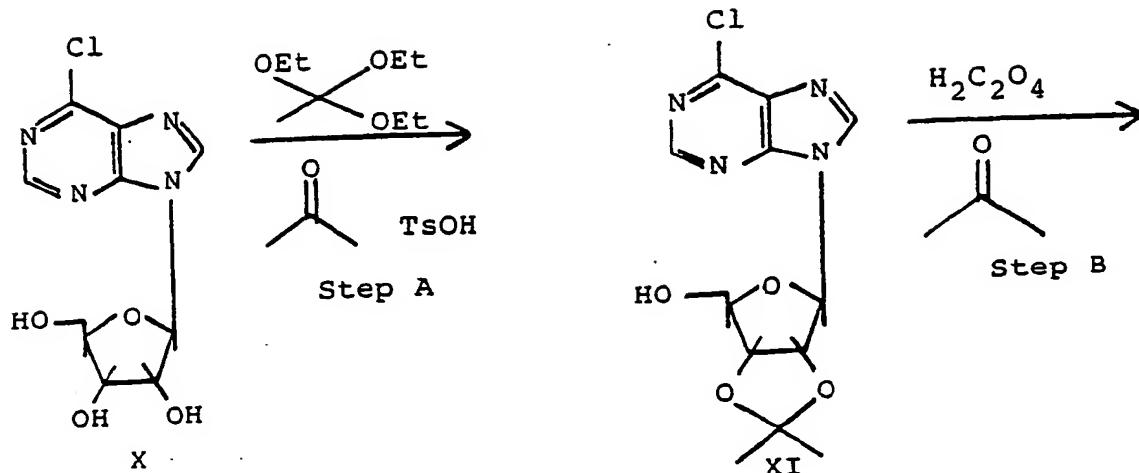


6-chloropurine riboside
 in the presence of
 triethylamine



Although the N⁶ sidechain is made as described above, a particularly preferred novel process to make the uronamide portion of the molecule of the compound I is also the present invention. It is shown as follows:
 5

-13-



-14-

The novel process shown above to make the uronamide portions on the compound of formula I is generally carried out by treating the compound of formula X with ethyl orthoformate and tosic acid in acetone, to give isopropylidene XI in 80-90% yields. Oxidation of XI with chromic acid in acetone gives the 5 uronic acid XII in 53-60% yield. This can be converted to acid XIII in 80% yield by treatment with an appropriate 10 2,2-diarylethylamine and triethylamine in ethanol, and then amidated with an appropriate primary amine and a condensing agent such as dicyclohexylcarbodiimide/1-hydroxybenzotriazole or N-methyl-2-fluoropyridinium tosylate/triethylamine, to give 15 the protected nucleoside XIV, which on acid hydrolysis, preferably with aqueous TFA at 0°C gives the desired nucleoside XV. Alternatively compound XIV can be generated from uronic acid XII, by amidation of the uronic acid moiety as described to give XIV followed by displacement of the C6-Cl under the same conditions as described previously.

Although this process is related to those previously claimed in World Appl. 8600310 following the procedure of J. Med. Chem., Vol. 23, pp. 313-9 (1986) it has several distinct advantages. In the present process the isopropylidenation of inosine is physically awkward whereas the X to XI transformation is operationally very simple. Furthermore the oxidation of inosine isopropylidene to the corresponding uronic acid according to previously known processes is also tedious, and in our hands never gave the claimed yields (=65%) but consistently lower yields (20-25%). The conversion of XI to XII was found to be reproducible in 50-60% yield, and the entire reaction can be carried out in 2-4 hours, a major 25 savings in time. We were unsuccessful in several attempts to 30 convert inosine isopropylidene-5'-uronate into intermediate XIV, under conditions claimed previously, whereas our procedures reproducibly allowed for XV (or XIV) to be produced from the corresponding uronic acids in 60-95% yields. Therefore, the present process unexpectedly provides a process 35 overall operationally much simpler than previously claimed processes, and that the complete process X to XV can be carried

-15-

out on a laboratory scale in 20-30% overall yield in 3 working days.

The starting materials in the above described processes to prepare the compounds of the formula I are generally known, commercially available or can be prepared by methods either known or analogous to those known.

Variations in the processes of the present invention are within the skill of an ordinary artisan. The products of the processes are isolated by conventional means such as extraction, distillation, chromatography and the like.

The compounds of formula I are now found to possess surprising and unexpected preference in binding A₂ adenosine receptors.

By molecular modeling the compounds of the present invention can be said to preferably bind to A₂ receptors. Such A₂ binding indicates a different mechanism of action from that previously indicated for adenosine derivatives known for common utilities. Such utilities in view of the novel A₂ binding preference is unexpected compared to the differing affinities for the A₁ and A₂ receptors indicated in the above cited U.S. Serial Number 756,922. Thus, the compounds of the present invention represent a novel mechanism of action which cannot be predicted from previously disclosed data. Further the demonstrated difference between A₂ and A₁ receptor binding is in the range of 1.5 to 35 fold. Additionally, activity in the animal tests of the present compounds exceeds that expected based on the measured A₁ receptor binding of these compounds and, therefore, is also surprising. Further among the present compounds, the effect of the compound of Example 19 is not reversed in the MAST test by an A₁ selective antagonist unlike selected compounds of examples from SN 756,922 noted above. Also, the compound of Example 19 is now found to have a different effect on dopamine receptors from selected compounds of the examples in USSN 756,922 again as noted above.

These compounds of formula I are active in animal tests which are predictive of neuroleptic activity for the treatment of major psychoses such as schizophrenia. The compounds of the

-16-

invention also have sedative/hypnotic properties and as such, are useful in the treatment of pain.

Additionally, the compounds of the present invention are useful in the treatment of congestive heart failure.

5 Particularly, the compounds of formula I are now found to possess vasodilator properties with a marked selectivity for coronary over peripheral vasculature and a positive inotropic effect which increases blood flow useful in the treatment of angina and congestive heart failure. For a similar effect with
10 an adenosine see patent application PD-3545.

The biological data from assays corresponding to those described in U.S. Serial Number 756,922 for the compounds in the present invention are summarized in the following tables for the noted examples described hereinafter.

15 Accordingly, the present invention also includes a pharmaceutical composition for treating psychoses, sleep disorders, pain, or cardiovascular diseases comprising a corresponding antipsychotic, sedative, analgesic, or cardiovascular disease effective amount of a compound of the
20 formula I as defined above with a pharmaceutically acceptable carrier.

Treatment of cardiovascular diseases means usefulness as antihypertensive agents for the treatment of high blood pressure. Also the treatment increases coronary blood flow, for example, as a vasodilator and therefore is useful in the
25 treatment of angina and congestive heart failure as well.

-17-

Table 1. Adenosine Receptor Binding -
 A_1 and A_2 Receptor Affinity (RBA1 and RBA2)

	Example	RBA1 IC ₅₀ (nM)	RBA2 IC ₅₀ (nM)
5	1	380	62
	2	1300	150
	3	40	9
	4	68	17
	5	400	230
10	6	100	27
	7	33	9
	8	20	10
	9	130	27
	10	10	6
15	11	53	9
	12	280	47
	13	3800	1600
	14	51	7.7
	15	46	17
20	16	63	44
	17	78	13
	18	2500	890
	19	207	6.7
	20	356	34
25	21	50	10
	22	57	7.8
	23	74	5.3
	24	280	8.2
	25	84	7.4
30	26	160	16
	27	500	19
	28	260	16
	29	170	4.5
	30	220	8.7

WO 88/03147

-18-

Example	RBA1 IC ₅₀ (nM)	RBA2 IC ₅₀ (nM)
31	3300	200
32	>100,000	3830
33	1540	41
34	1930	58
5	330	6.7
35	574	13.6
36		

Table 2. MAST Values

10	Example	Dose (IP ¹) mg/kg	% IMA ²	% SFO ³
1	1	3	10	0
		10	41	0
		30	67	0
15	2	3	22	0
		10	50	0
		30	52	0
20	3	1	27	0
		3	67	0
		10	73	0
25	4	3	30	0
		10	59	0
		30	58	0
25	5	3	4	0
		10	26	0
		30	26	0

-19-

Example	Dose (IP ¹) mg/kg	% IMA ²	% SFO ³
6	3	44	0
	10	87	0
	30	90	11
5	7	11	0
	1.0	56	0
	3.0	79	0
	10	88	0
10	8	47	0
	10	63	0
	30	73	0
15	9	35	0
	10	51	0
	30	81	0
20	10	57	0
	3	61	0
	10	78	0
25	11	8	0
	0.1	14	0
	0.3	58	0
	1.0	71	0
	3.0	80	0
	10	83	0
25	12	28	0
	10	46	0
	30	78	0

-20-

Example	Dose (IP ¹) mg/kg	% IMA ²	% SFO ³
14	0.3	-2	0
	1	39	0
	3	60	0
	10	89	0
	30	84	0
15	3	46	0
	10	84	0
	30	81	0
16	3	1	0
	10	52	0
	30	70	0
17	1	25	0
	3	64	0
	10	77	0
19	1	32	0
	3	58	0
	10	81	0
	30	83	0
20	3	8	0
	10	44	0
	30	61	0
21	3	51	0
	10	60	0
	30	65	0
25			

-21-

Example	Dose (IP ¹) mg/kg	% IMA ²	% SFO ³
5	22 1	48	0
	3	68	0
	10	88	0
	30	82	0
10	23 0.3	14	0
	1	53	0
	3	74	0
	10	80	0
	30	79	11
15	24 3	51	0
	10	71	0
	30	78	0
20	25 0.3	29	0
	1	48	0
	3	78	0
	10	90	0
	30	91	0
25	26 3	11	0
	10	63	0
	30	65	0
25	27 3	26	0
	10	41	0
	30	53	0
25	28 3	17	0
	10	34	0
	30	58	0

-22-

Example	Dose (IP ¹) mg/kg	% IMA ²	% SFO ³
33	3	11	0
	10	30	0
	30	49	0
34	3	38	0
	10	64	0
	30	66	0
35	0.3	10	0
	1.0	52	0
	3	68	0
	10	82	22
	30	90	0
36	3	44	0
	10	68	0
	30	77	0
15			

¹Intraperitoneal²Inhibition of mouse activity³Screen fall off (% inhibition of screen test failure)Table 3. Sidman Rat ED₅₀s

20

Example 11	2.1 mg/kg
Example 19	3.2 mg/kg
Example 22	5.0 mg/kg
Example 23	3.5 mg/kg
Example 24	8.5 mg/kg

-23-

Table 4. AHP3 Data

	Example	Dose mg/kg	Max BP+
	1	10	21%
5	2	10	20%
	3	10	17%
	4	10	13%
	6	10	33%
	7	3	13%
10	8	10	22%
	9	10	43%
	11	10	29%
	17	10	23%
	19	10	22%
	20	10	32%
15	21	10	14%
	22	10	13%
	23	10	40%
	24	10	34%
	26	10	16%
20	27	10	12%

Accordingly, the present invention further includes a method for treating psychoses, sleep disorders, pain, or cardiovascular diseases in mammals suffering therefrom comprising administering to such mammals either orally or parenterally a corresponding pharmaceutical composition having a compound of the formula I as defined above in appropriate dosage form.

The compositions and methods of administration are as understood by the present state of the art, for example, as disclosed in U.S. Serial Number 756,922.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 500 mg preferably to 5 to 100 mg according to the particular

-24-

application and the potency of the active ingredient. The compositions can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as described above, the mammalian dosage range for a 70 kg subject is from 0.01 to 100 mg/kg of body weight per day or preferably 0.1 to 50 mg/kg of body weight per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed.

Determination of the proper dosage for a particular situation is with the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following Examples further illustrate the invention.

EXAMPLE 1

20 N,6-(2-(2,6-Dimethylphenyl)-2-phenylethyl)adenosine

a) E,2-(2,6-Dimethylphenyl)nitroethene

Aqueous sodium hydroxide (2.5 M, 20 ml) was added dropwise over 15 min to a solution of 2,6-dimethylbenzaldehyde (6.7 g, 50 mmol) and nitromethane (3.1 g, 50 mmol) in methanol (25 ml) stirred under N₂ at 0°C. After a further 15 mins the reaction mixture was quenched by pouring onto dilute hydrochloric acid (0.5 M, 100 ml) and extracting with ether (3x25 ml). The combined extracts were washed with water (2x25 ml) and saturated brine (25 ml) and dried (MgSO₄). The solvent was removed under reduced pressure and the residual yellow oil was dissolved in CH₂Cl₂ (150 ml) and stirred under N₂ at 0°C. Mesyl chloride (5.7 g, 50 mmol) in CH₂Cl₂ (25 ml) and then triethylamine (10.1 g, 100 mmol) in CH₂Cl₂ (25 ml) were added sequentially to the solution. After 1.5 hr the reaction

-25-

5 mixture was poured onto dilute hydrochloric acid (0.5 M, 200 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 ml). The combined organic phases were washed with water (2x50 ml), saturated brine (50 ml), and dried (MgSO_4). The solvent was removed under reduced pressure to give the nitrostyrene (8.33 g, 96%) as a light brown oil.
Nmr (CDCl_3) δ 8.22 (1H, d, $J=14$ Hz), 6.9-7.4 (4H, m), 2.41 (6H, s).

b) 2-(2,6-Dimethylphenyl)-2-phenylethylamine

10 Phenylmagnesium bromide (2.9 M in ether, 5 ml, 14.5 mmol), was added dropwise over 10 min to a solution of E,2-(2,6-dimethylphenyl)nitroethene (1.77 g, 10 mmol) in toluene (50 ml) stirred under N_2 at -30°. The solution reddened, and after a further 15 min at -30° the reaction was
15 quenched by addition of dilute hydrochloric acid (0.4 M, 50 ml). The layers were separated, and the aqueous layer was extracted with toluene (25 ml). The combined organic phases were washed with water (25 ml, emulsions usual at this step), saturated brine (25 ml), and dried (MgSO_4). The solvent was removed under reduced pressure to give the crude diarylnitroethane (2.05 g) as a yellow oil. This was dissolved
20 in ether (25 ml) and added dropwise over 20 min to a suspension of LiAlH_4 (1.11 g, 30 mmol) in ether (100 ml) stirred under N_2 at 25°. Vigorous gas evolution and mild exotherm! After 3 hr
25 the reaction was quenched by cautious, sequential, dropwise addition of water (1 ml), aqueous sodium hydroxide solution (10% w/v, 1 ml) and water (3 ml). Vigorous gas evolution and exotherm! The mixture was vacuum filtered, and the residue was washed with ether (100 ml). The combined filtrates were
30 extracted with dilute hydrochloric acid (0.1 M, 2x100 ml). The aqueous layer was washed with ether (2x50 ml), made basic with NaOH pellets (1.0 g, 25 mmol) and extracted with ether (3x25 ml). The combined extracts were washed with water (2x25 ml, (frequent emulsions)), saturated brine (25 ml), and dried (MgSO_4). The solvent was removed under reduced pressure to give the desired amine (1.00 g, 44%) as a pale yellow oil.

-26-

Nmr (CDCl_3) δ 7.1-7.3 (5H, m), 6.9-7.1 (3H, m), 4.56 (1H, d of d, $J=6,8$ Hz), 3.61-3.35 (2H, ABq of ds, $J_{AB} = 12.5$ Hz, $J_{d}=6,8$ Hz), 2.18 (6H, s), 1.16 (2H, br s).

c) N,6-(2-(2,6-Dimethylphenyl)-2-phenethyl)adenosine

5 6-Chloropurine riboside (1.28 g, 4.4 mmol), 2-(2,6-dimethylphenyl)-2-phenylethylamine (1.00 g, 4.4 mmol) and triethylamine (0.89 g, 8.8 mmol) were refluxed in ethanol (40 ml) under N_2 with stirring for 15 h. The solvent was removed under reduced pressure to give a pale brown solid foam, 10 which was added to ethyl acetate (50 ml), washed with water (2x25 ml, emulsion!), saturated brine (25 ml), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residual solid foam was purified by silica gel chromatography eluting with 5% CH_3OH in CHCl_3 . The solvent was 15 removed under reduced pressure to give the desired nucleoside (1.44 g, 67%) as an offwhite solid foam, mp 112-124°C.

Calcd. for $\text{C}_{26}\text{H}_{29}\text{N}_5\text{O}_4 \cdot 0.13 \text{CHCl}_3$

C, 63.91; H, 5.93; N, 14.27; Cl, 2.82

Found C, 63.42; H, 6.05; N, 14.26; Cl, 2.83.

20

EXAMPLE 2

N,6-(2-(2,6-Dimethylphenyl)-2-(4-methylphenyl)ethyl)adenosine

25 2-(2,6-Dimethylphenyl)-2-(4-methylphenyl)ethylamine (0.92 g, 38%) was prepared from E,2-(2,6-dimethylphenyl)nitroethene (1.77 g, 10 mmol, see Example 1), 4-bromotoluene (2.56 g, 15 mmol) and Mg (0.36 g, 15 mmol), followed by LiAlH_4 reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.20 g, 62%) was prepared from the amine (0.92 g, 3.8 mmol) 6-chloropurine riboside (1.11 g, 3.8 mmol) and triethylamine (0.81 g, 8 mmol) as a pale yellow solid foam, 30 mp 113-22°C as described in Example 1.

-27-

EXAMPLE 3

N,6-(2-(3,5-Dimethylphenyl)-2-phenethyl)adenosine

The nitrostyrene (2.25 g, 79%) was prepared from 3,5-dimethylbenzaldehyde (2.1 g, 0.16 mole) and nitromethane (0.9 g, .016 mole) as described in Example 1.

The amine (0.57 g, 21%) was prepared from E,2-(3,5-dimethylphenyl)nitroethene (2.25 g, .012 mole), phenylmagnesium bromide (6.3 ml, .019 mole), followed by LiAlH₄ reduction (1.38 g, .036 mole) as described in Example 1.

The nucleoside (0.62 g, 47%) was prepared from the amine (0.57 g, .0025 mole), 6-chloropurine riboside (0.66 g, .0023 mole) and triethylamine (0.3 ml, .0025 mole) as a solid, mp 94-97°C as described in Example 1.

EXAMPLE 4

N,6-(2-Naphth-1-yl-2-phenethyl)adenosine

The nitrostyrene (19.38 g, 97%) was prepared from 1-naphthaldehyde (15.62 g, 100 mmol) and nitromethane (6.1 g, 100 mmol) as described in Example 1.

The amine (3.78 g, 59%) was prepared from E,2-naphth-1-ylnitroethene (4.88 g, 25 mmol), and phenylmagnesium bromide (27 mmol), followed by LiAlH₄ reduction (2.22 g, 60 mmol) as described in Example 1.

The nucleoside (3.43 g, 67%) was prepared from 2-naphth-1-yl-2-phenethylamine (2.56 g, 10 mmol), 6-chloropurine riboside (2.87 g, 10 mmol) and triethylamine (2.0 g, 20 mmol) as a white powder, mp 120-8°C as described in Example 1.

EXAMPLE 5

N,6-(2-(3,5-Dichlorophenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine

The nitrostyrene (8.48 g, 97%) was prepared from 3,5-dichlorobenzaldehyde (7.00 g, 40 mmol) and nitromethane (2.44 g, 40 mmol) as described in Example 1.

The amine (1.39 g, 47%) was prepared from E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, 10 mmol),

-28-

2,6-dimethylbromobenzene (2.78 g, 15 mmol) and Mg (0.36 g, 15 mmol) followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.05 g, 77%) was prepared from
5 2-(3,5-dichlorophenyl)-2-(2,6-dimethylphenyl) ethylamine (1.39 g, 4.7 mmol), 6-chloropurine riboside (1.35 g, 4.7 mmol) and triethylamine (0.95 g, 9.4 mmol) as a white solid foam, mp 125-35°C as described in Example 1.

EXAMPLE 6

N,6-(2-(2,6-Dichlorophenyl)-2-phenethyl)adenosine

The nitrostyrene (10.18 g, 93.4%) was prepared from 2,6-dichlorobenzaldehyde (8.75 g, 50 mmol) and nitromethane (3.05 g, 50 mmol) as described in Example 1.

The amine (1.95 g, 45%) was prepared from
15 E,2-(2,6-dichlorophenyl)nitroethene (3.27 g, 15 mmol) and phenylmagnesium bromide (18 mmol) followed by LiAlH₄ reduction (2.22 g, 60 mmol) as described in Example 1.

The nucleoside (1.55 g, 61%) was prepared from the amine (1.48 g, .0056 mole), 6-chloropurine riboside (1.40 g, 20 .0049 mole) and triethylamine (1.4 ml, .01 mole) as a solid, mp 102-12°C as described in Example 1.

EXAMPLE 7

N,6-(2-(3,5-Dichlorophenyl)-2-phenethyl)adenosine

The amine (1.09 g, 41%) was prepared from
25 E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, see Example 5) and phenylmagnesium bromide (15 mmol), followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.63 g, 77%) was prepared from
30 2-(3,5-dichlorophenyl)-2-phenethylamine (1.09 g, 4.1 mmol) 6-chloropurine riboside (1.08 g, 4.1 mmol) and triethylamine (0.81 g, 8 mmol) as an offwhite solid foam, mp 110-115°C as described in Example 1.

-29-

EXAMPLE 8

N,6-(2-(3-Chlorophenyl)-2-(3,5-dichlorophenyl)ethyl)adenosine

The amine (1.08 g, 36%) was prepared from E,2-(3,5-dichlorophenyl)nitroethene (2.18 g, 10 mmol, see Example 5), 3-bromochlorobenzene (3.83 g, 20 mmol) and Mg (0.36 g, 15 mmol), followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.53 g, 77%) was prepared from 2-(3-chlorophenyl)-2-(3,5-dichlorophenyl)ethylamine (1.08 g, 3.6 mmol), 6-chloropurine riboside (1.05 g, 3.6 mmol) and triethylamine (0.71 g, 7 mmol) as a white solid foam, mp 107-23°C as described in Example 1.

EXAMPLE 9

N,6-(2-(3-Chlorophenyl)-2-(2,6-dichlorophenyl)ethyl)adenosine

The amine (1.21 g, 40%) was prepared from E,2-(2,6-dichlorophenyl)nitroethene (2.18 g, 10 mmol, see Example 6), 3-bromochlorobenzene (3.83 g, 20 mmol) and Mg (0.36 g, 15 mmol) followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (0.84 g, 38%) was prepared from 2-(3-chlorophenyl)-2-(2,6-dichlorophenyl)ethylamine (1.21 g, 4 mmol), 6-chloropurine riboside (1.15 g, 4 mmol) and triethylamine (0.81 g, 8 mmol) as a pale yellow solid foam, mp 113-25°C as described in Example 1.

25

EXAMPLE 10

N,6-(2-(3-Chlorophenyl)-2-(3,5-dimethoxyphenyl)ethyl)adenosine

The nitrostyrene (14.41 g, 97%) was prepared from 3,5-dimethoxybenzaldehyde (12.2 g, 73 mmol) and nitromethane (4.6 g, 75 mmol) as described in Example 1.

30

The amine (0.46 g, 26%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (1.25 g, .006 mole), 3-chlorobromobenzene (2.9 ml, .025 mole), magnesium (0.48 g, .02 mole), followed by LiAlH₄ reduction (1.40 g, .037 mole) as described in Example 1.

-30-

The nucleoside (0.36 g, 44%) was prepared from the amine (0.40 g, .0014 mole), 6-chloropurine riboside (0.40 g, .0014 mole) and triethylamine (0.2 ml, .0015 mole) as an offwhite solid, mp 81-86°C as described in Example 1.

5

EXAMPLE 11

N,6-(2-(3,5-Dimethoxyphenyl)-2-phenethyl)adenosine

The amine (10.4 g, 59%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (14.41 g, 68 mmol, see Example 10) and phenylmagnesium bromide (100 mmol), followed by LiAlH₄ reduction (7.77 g, 210 mmol) as described in Example 1.

The nucleoside (17.14 g, 83%) was prepared from the amine (10.4 g, 40 mmol), 6-chloropurine riboside (11.5 g, .40 mmol), and triethylamine (8.08 g, 80 mmol) as an offwhite solid foam, mp 97-105°C as described in Example 1.

15

EXAMPLE 12

N,6-(2-(2,5-Dimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (7.65 g, 49%) was prepared from 2,5-dimethoxybenzaldehyde (12.5 g, .075 mole) and nitromethane (4.58 g, .075 mole) as described in Example 1.

20

The amine (1.04 g, 21%) was prepared from E,2-(2,5-dimethoxyphenyl)nitroethene (7.0 g, .033 mole), phenylmagnesium bromide (15.8 ml, .047 mole), followed by LiAlH₄ reduction (2.90 g, .076 mole) as described in Example 1.

25

The nucleoside (0.43 g, 23%) was prepared from the amine (1.04 g, .004 mole), 6-chloropurine riboside (1.03 g, .0036 mole) and triethylamine (0.5 ml, .004 mole) as a solid, mp 96-100°C as described in Example 1.

N,6-(2-(2,6-Dimethoxyphenyl)-2-phenethyl)adenosine

30

The nitrostyrene (6.87 g, 82%) was prepared from 2,6-dimethoxybenzaldehyde (6.5 g, 37 mmol) and nitromethane (2.29 g, 37 mmol) as described in Example 1.

-31-

The amine (0.49 g) was prepared in very impure form from E,2-(2,6-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol) and phenyl lithium (15 mmol in ether/cyclohexane), followed by LiAlH₄ (1.11 g, 30 mmol) as described in Example 1.

5 The nucleoside (0.29 g, 6% based on nitrostyrene) was prepared from crude 2-(2,6-dimethoxyphenyl)-2-phenethylamine (0.49 g), 6-chloropurine riboside (0.58 g, 2 mmol) and triethylamine (0.40 g, 4 mmol), as described in Example 1, except for an additional purification on preparative silica gel chromatography plates, eluting twice with 8% CH₃OH in CHCl₃, as 10 yellow brown solid foam, mp 112-21°C.

EXAMPLE 14

N,6-(2-(2-Methoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine

15 The nitrostyrene (32.5 g, 91%) was prepared from 2-methoxybenzaldehyde (27.2 g, 0.2 mole) and nitromethane (12.2 g, 0.2 mole) as described in Example 1.

20 The amine (1.81 g, 28%) was prepared from E,2-(2-methoxyphenyl)nitroethene (4.48 g, .025 mole), 3-methoxybromobenzene (6.3 ml, .05 mole), magnesium (0.97 g, .04 mole), followed by LiAlH₄ reduction (2.43 g, .064 mole) as described in Example 1.

25 The nucleoside (1.20 g, 37%) was prepared from the amine (1.80 g, .007 mole), 6-chloropurine riboside (1.72 g, .006 mole) and triethylamine (0.9 ml, .0066 mole) as a beige foam, mp 103-05°C as described in Example 1.

EXAMPLE 15

N,6-(2-(3,4-Dimethoxyphenyl)-2-phenethyl)adenosine

30 The nitrostyrene (12.23 g, 39%) was prepared from 3,4-dimethoxybenzaldehyde (24.9 g, .15 mole) and nitromethane (9.15 g, .15 mole) as described in Example 1.

35 The amine (1.18 g, 12%) was prepared from E,2-(3,4-dimethoxyphenyl)nitroethene (8.82 g, .042 mole), phenylmagnesium bromide (20.7 ml, .06 mole), followed by LiAlH₄ reduction (2.55 g, .067 mole) as described in Example 1.

-32-

The nucleoside (1.24 g, 59%) was prepared from the amine (1.16 g, .0045 mole), 6-chloropurine riboside (1.09 g, .0038 mole) and triethylamine (0.6 mole, .0042 mole) as a solid, mp 96-104°C as described in Example 1.

5

EXAMPLE 16

N,6-(2-(3,5-Diethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (2.73 g, 88%) was prepared from 3,5-diethoxybenzaldehyde (2.68 g, .014 mole) and nitromethane (0.86 g, .014 mole) as described in Example 1.

10

The amine (1.25 g, 37%) was prepared from E,2-(3,5-diethoxyphenyl)nitroethene (2.73 g, .012 mole), phenylmagnesium bromide (6.3 ml, .019 mole), followed by LiAlH₄ reduction (1.17 g, .031 mole) as described in Example 1.

15

The nucleoside (1.62 g, 74%) was prepared from the amine (1.23 g, .004 mole), 6-chloropurine riboside (1.15 g, .004 mole) and triethylamine (0.6 ml, .0044 mole) as a white foam, mp 88-93°C as described in Example 1.

EXAMPLE 17

N,6-(2-(3,5-Dimethoxyphenyl)-2-thien-2-yl)ethyl)adenosine

20

The amine (1.60 g, 27%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (5.23 g, .025 mole, see Example 10), 2-bromothiophene (5.2 ml, .05 mole) and magnesium (0.96 g, .04 mole), followed by LiAlH₄ reduction (3.80 g, .10 mole) as described in Example 1.

25

The nucleoside (1.61 g, 59%) was prepared from the amine (1.38 g, .0052 mole), 6-chloropurine riboside (1.35 g, .0047 mole), and triethylamine (0.7 ml, .0052 mole) as a solid, mp 80-83°C as described in Example 1.

EXAMPLE 18

30

N,6-(2-(3,5-Dimethoxyphenyl)-2-naphth-1-ylethyl)adenosine

The amine (0.48 g, 14%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (2.22 g, .011 mole, see

-33-

Example 10), 1-bromonaphthalene (3.1 ml, .022 mole), and magnesium (0.43 g, .018 mole), followed by LiAlH₄ reduction (0.90 g, .024 mole) as described in Example 1.

The nucleoside (0.22 g, 25%) was prepared from the amine
5 (0.48 g, .0016 mole), 6-chloropurine riboside (0.40 g,
.0014 mole) and triethylamine (0.2 ml, .0015 mole) as a solid,
mp 114-118.5°C as described in Example 1.

EXAMPLE 19

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine

10 The amine (1.90 g, 67%) was prepared from
E,2-(3,5-dimethoxy)nitroethene (2.09 g, 10 mmol, see Example
10), 2-bromotoluene (2.57 g, 15 mmol) and magnesium (0.36 g,
15 mmol), followed by LiAlH₄ reduction (1.11 g, 30 mmol) as
described in Example 1.

15 The nucleoside (2.85 g, 79%) was prepared from
2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (1.90 g,
6.7 mmol), 6-chloropurine riboside (1.94 g, 6.7 mmol) and
triethyl amine (1.31 g, 13 mmol) as an offwhite solid foam, mp
105-12°C as described in Example 1.

EXAMPLE 20

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2,6-dimethylphenyl)ethyl) adenosine

20 The amine (2.05 g, 71%) was prepared from
E,2-(3,5-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol, see
Example 10), 2,6-dimethylbromobenzene (2.78 g, 15 mmol) and
magnesium (0.36 g, 15 mmol), followed by LiAlH₄ reduction
(1.11 g, 30 mmol) as described in Example 1.

25 The nucleoside (2.23 g, 79%) was prepared from
2-(3,5-dimethoxyphenyl)-2-(2,6-dimethylphenyl) ethylamine
(2.05 g, 7 mmol), 6-chloropurine riboside (2.05 g, 7 mmol) and
triethylamine (1.41 g, 14 mmol) as a white solid foam, mp
107-17°C as described in Example 1.

-34-

EXAMPLE 21

N,6-(2-(3,5-Dimethoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine

The amine (1.70 g, 59%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (2.09 g, 10 mmol, see Example 10), 3-bromoanisole (2.80 g, 15 mmol) and magnesium (0.48 g, 20 mmol) followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (2.42 g, 76%) was prepared from 2-(3,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethylamine (1.70 g, 6 mmol), 6-chloropurine riboside (1.72 g, 6 mmol) and triethylamine (1.21 g, 12 mmol) as a beige solid foam, mp 90-101°C as described in Example 1.

EXAMPLE 22

N,6-(2-(3,4,5-Trimethoxyphenyl)-2-phenethyl)adenosine

The nitrostyrene (31.21 g, 63%) was prepared from 3,4,5-trimethoxybenzaldehyde (40.8 g, .21 mole) and nitromethane (12.4 g, .20 mole) as described in Example 1.

The amine (0.84 g, 4%) was prepared from E,2-(3,4,5-trimethoxyphenyl)nitroethene (15.72 g, .066 mole), phenylmagnesium bromide (29.6 ml, .089 mole), followed by LiAlH₄ reduction (1.83 g, .048 mole) as described in Example 1.

The nucleoside (1.25 g, 85%) was prepared from the amine (0.82 g, .0029 mole), 6-chloropurine riboside (0.75 g, .0026 mole), and triethylamine (0.4 ml, .0029 mole) as a solid, mp 95-99°C as described in Example 1.

EXAMPLE 23

N,6-(2-(3,5-Dimethoxyphenyl)-2-(2-methoxyphenyl)ethyl)adenosine

The amine (5.26 g, 46%) was prepared from E,2-(3,5-dimethoxyphenyl)nitroethene (8.36 g, .04 mole, see Example 10), 2-methoxybromobenzene (10.2 ml, .08 mole), and magnesium (1.57 g, .064 mole), followed by LiAlH₄ reduction (5.98 g, .16 mole) as described in Example 1.

The nucleoside (5.15 g, 90%) was prepared from the amine (3.16 g, .011 mole), 6-chloropurine riboside (2.86 g, .01 mole)

- 35 -

and triethylamine (1.4 ml, .011 mole) as a solid, mp 93-97°C as described in Example 1.

EXAMPLE 24

N,6-(2-(3,4,5-Trimethoxyphenyl)-2-(methylphenyl)ethyl)adenosine

5 The amine (1.01 g, 31%) was prepared from
E,2-(3,4,5-trimethoxyphenyl)nitroethene (2.39 g, 10 mmol, see
Example 22), 2-bromotoluene (2.57 g, 15 mmol), and magnesium
(0.36 g, 15 mmol) followed by LiAlH₄ reduction (1.11 g,
30 mmol) as described in Example 1.

10 The nucleoside (1.16 g, 66%) was prepared from
2-(3,4,5-trimethoxyphenyl)-2-(2-methylphenyl ethylamine
(1.01 g, 3 mmol), 6-chloropurine riboside (0.89 g, 3 mmol) and
triethylamine (0.61 g, 6 mmol) as a white solid foam, mp
107-15°C as described in Example 1.

15

EXAMPLE 25

N,6-(2-(2-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl)
adenosine

20 The amine (0.70 g, 9%) was prepared from
E,2-(3,4,5-trimethoxyphenyl)nitroethene (5.98 g, .025 mole, see
Example 22), 2-methoxybromobenzene (6.4 ml, .05 mole),
magnesium (0.97 g, .04 mole), followed by LiAlH₄ reduction
(2.43 g, .064 mole) as described in Example 1.

25 The nucleoside (0.67 g, 54%) was prepared from the amine
(0.70 g, .0022 mole), 6-chloropurine riboside (0.57 g,
.002 mole), and triethylamine (0.3 ml, .0022 mole) as a grey
foam, mp 99-104°C as described in Example 1.

EXAMPLE 26

N,6-(2-(2-Methoxyphenyl)-2-(3-(trifluoromethyl)phenyl)ethyl)
adenosine

30 The nitrostyrene (9.84 g, 91%) was prepared from
3-(trifluoromethyl)benzaldehyde (8.7 g, 50 mmol) and
nitromethane (3.1 g, 50 mmol) as described in Example 1.

-36-

The amine (1.72 g, 57%) was prepared from E,2-(3-(trifluoromethyl)phenyl)nitroethene (2.17 g, 10 mmol), 2-bromoanisole (2.81 g, 15 mmol) and magnesium (0.36 g, 15 mmol) as described in Example 1.

5 The nucleoside (2.22 g, 71%) was prepared from 2-(2-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl) ethylamine (1.72 g, 5.7 mmol), 6-chloropurine riboside (1.78 g, 6.2 mmol) and triethylamine (1.2 g, 12 mmol) as a pale yellow solid foam, mp 100-108°C as described in Example 1.

10

EXAMPLE 27

N,6-(2-(2-Methoxyphenyl)-2-(3,5-bis(trifluoromethyl)phenyl)ethyl)adenosine

15 The nitrostyrene (5.48 g, 87%) was prepared from 3,5-bis(trifluoromethyl)benzaldehyde (5.77 g, 22 mmol) and nitromethane (2.69 g, 44 mmol) as described in Example 1.

20 The amine (0.76 g, 42%) was prepared from E,2-(3,5-bis(trifluoromethyl)phenyl)nitroethene (1.43 g, 5 mmol), 2-bromoanisole (1.39 g, 7.5 mmol), and magnesium (0.18 g, 7.5 mmol) followed by LiAlH₄ reduction (0.55 g, 15 mmol) as described in Example 1.

25 The nucleoside (0.97 g, 75%) was prepared from 2-(2-methoxyphenyl)-2-(3,5-bis(trifluoromethyl)phenyl)ethylamine (0.76 g, 2.1 mmol), 6-chloropurine riboside (0.61 g, 2.1 mmol), and triethylamine (0.40 g, 4 mmol) as a white solid foam, mp 105-12°C as described in Example 1.

EXAMPLE 28

N,6-(2-(3,5-Bis(trifluoromethyl)phenyl-2-phenethyl)adenosine

30 The amine (0.92 g, 27%) was prepared from E,2-(3,5-bis(trifluoromethyl)phenyl)nitroethene (2.85 g, 10 mmol, see Example 27) and phenylmagnesium bromide (15 mmol) followed by LiAlH₄ reduction (1.11 g, 30 mmol) as described in Example 1.

The nucleoside (1.20 g, 75%) was prepared from 2-(3,5-bis(trifluoromethyl)phenyl)-2-phenethylamine (0.92 g,

-37-

2.7 mmol), 6-chloropurine riboside (0.80 g, 2.7 mmol) and triethylamine (0.60 g, 6 mmol) as a pale yellow solid foam, mp 99-105°C as described in Example 1.

EXAMPLE 29

5 N⁶-((--)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine

(±) 2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (40.65 g, 0.15 mol) and [2R,3R]dibenzoyl tartaric acid monohydrate (56.4 g, 0.15 mol) were dissolved in refluxing EtOH (=700 ml) and then recrystallized 5 times, seeding with crystals of optically enriched salt (produced in 94% EE by recrystallizing a small sample 10 times) to give 5.78 g of salt, EE = 93.4%, mp 175.5-177°C, $[\alpha]_D^{23}$ (MeOH) -93.5°. The ammonium salt (5.00 g) was partitioned between dilute NaOH solution (1N, 30 ml) and ether (50 ml). The layers were separated and the aqueous layer was extracted with further ether (25 ml). The combined organic phases were washed with water (2x25 ml), saturated brine (25 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give (-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.08 g) as a cloudy pale yellow oil $[\alpha]_D^{23}$ (MeOH) -57.4°, EE = 93.4%.

The nucleoside (3.53 g, 90%) was prepared from (-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (2.02 g, 7.45 mmol), 6-chloropurine riboside (2.16 g, 7.5 mmol) and NEt_3 (1.51 g, 15 mmol) in ethanol (70 ml) at reflux stirred under N_2 for 18 hours. On cooling the desired nucleoside crystallized out (3.53 g, 90%) as white microscopic needles, mp 195-197°C. Rotation $[\alpha]_D^{23}$ (DMSO) -78.1°. Diastereoisomeric excess ≥ 90%.

-38-

EXAMPLE 30

N⁶-((+)-2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)

adenosine

The mother liquors, from the first crystallization of
5 (+) 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl ammonium
di-o-benzoyl[2R,3R]tartrate, described in Example 29, were
evaporated to dryness. It was then stirred with dilute NaOH
solution (0.4 M, 500 ml) and ether (100 ml) until all solid had
dissolved. The layers were separated and the aqueous layer was
10 extracted with further ether (2x100 ml). The combined ethereal
extracts were washed with NaOH solution (0.25 M, 100 ml), water
(100 ml), saturated brine (100 ml), and dried ($MgSO_4$). The
solvent was removed under reduced pressure to give
2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (17.2 g)
15 2:1 enriched in the (+) enantiomer. This was combined with
D-dibenzoyltartrate·H₂O (23.88 g, 63.5 mmol) and recrystallized
three times from ethanol, seeding with crystals of optically
enriched salt, to give 6.60 g of salt. EE = 91%, mp 169-71°C,
20 $[\alpha]_D^{23}$ (MeOH) +96°. The salt (5.00 g) was partitioned between
NaOH solution (1 M, 30 ml) and ether (50 ml). The layers were
separated, and the ethereal layer was extracted with further
ether (25 ml). The combined organic phase was washed with
water (2x25 ml), saturated brine (25 ml), and dried ($MgSO_4$).
The solvent was removed under reduced pressure to give
25 (+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine
(2.09 g) as a cloudy pale yellow oil. $[\alpha]_D^{23}$ (MeOH) +53.3°,
EE = 87% (estimated).

The nucleoside was prepared from (+)-2-(3,5-dimethoxy-
phenyl)-2-(2-methylphenyl)ethylamine (2.03 g, 7.5 mmol)
30 6-chloropurine riboside (2.16 g, 7.5 mmol) and NET₃ (1.51 g,
15 mmol) in ethanol at reflux stirring under N₂ for 18 hours.
The solvent was removed under reduced pressure, the residue
added to water (50 ml) and extracted with ethyl acetate
(2x25 ml). The combined organic phases were washed with water
35 (25 ml), saturated brine (25 ml), and dried ($MgSO_4$). The
solvent was removed under reduced pressure, and the residue was

recrystallized from EtOH (25 ml) at 0°C to give
N⁶-((+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)
adenosine (2.86 g, 74%) as white needles, mp 168-169°C.
Rotation [α]_D²³ (DMSO) -5.5°. Diastereoisomeric excess 80%.

5

EXAMPLE 31

5'-Bromo-5'-deoxy-N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methyl-

phenyl)ethyl)adenosine

A solution of 5'-bromo-5'-deoxy-S-phenylthiocinosine-
S,S-dioxide-2',3'-di-o-isopropylidene (3.0 g, 6 mmol),
10 2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (1.83 g,
6 mmol) and NEt₃ (1.21 g, 12 mmol) was stirred in CHCl₃ (30 ml)
under N₂ at 25°C for 40 hours. The mixture was poured onto
NaH₂PO₄ solution (0.4 M, 50 ml), the layers separated, and the
aqueous layer extracted with further CHCl₃ (30 ml). The
15 organic extracts were washed with water (2x30 ml), saturated
brine (30 ml), and dried (MgSO₄). The solvent was removed
under reduced pressure, and the residual solid foam was added
to 10% aqueous TFA (10 ml) and stirred under N₂ at 0°C for 45
minutes. The reaction mixture was poured onto Na₂CO₃ solution
20 (1 M, 200 ml) and extracted with EtOAc (3x50 ml). The combined
extracts were washed with water (2x25 ml), saturated brine
(25 ml), and dried (MgSO₄). The solvent was removed under
reduced pressure and the residue was purified by flash
chromatography on silica gel (225 g) eluting with 5% MeOH in
25 CHCl₃ to give 5'-bromo-5'-deoxy-N⁶-(2-(3,5-dimethoxyphenyl)-
2-(2-methylphenyl)ethyl)adenosine (2.07 g, 56%) as a pale
yellow solid foam, mp 76-91°C.

-40-

EXAMPLE 32

N⁶-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine
5'-uronic acid

6-Chloropurine riboside-2',3'-di-o-isopropylidene

5 Triethyl orthoformate (59.2 g, 0.4 mol) was added to a suspension of 6-chloropurine riboside (28.75 g, 0.10 mol) and tosic acid monohydrate (18 g, 0.095 mol) in acetone (1 L) stirred under N₂ at 25°. After 3 hours the now clear solution was concentrated under reduced pressure, and the residue was
10 poured onto K₂HPO₄ solution (26.1 g in 800 ml) and extracted with ethyl acetate (2x200 ml). The combined extracts were washed with water (2x100 ml), saturated brine (100 ml), and dried (MgSO₄). The solvent was removed under reduced pressure to give 6-chloropurine riboside-2',3'-di-o-isopropylidene
15 (28.5 g, 87%) as a light yellow crystalline solid, mp 155-158°C.

6-Chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid

20 A solution of chromic acid (2 M) in aqueous sulfuric acid (3 M, 100 ml) was added over 1 hour to a partial solution of 6-chloropurine riboside-2',3'-di-o-isopropylidene (32.65 g, 100 mmol) in acetone (500 ml) stirred under N₂ at 25° without cooling. After a further 15 minutes the mixture was celite filtered, and the residue was rinsed with EtOAc (2x250 ml).
25 The combined filtrates were washed with Na₂S₂O₅ solution (0.5 M, 50 ml) and water (3x50 ml). The organic phase was extracted with NaOH solution (0.5 M, 250 mL). The basic extract was washed with EtOAc (200 ml) and acidified with concentrated HCl. The yellow oil was extracted with ethyl acetate (3x100 ml), and the organic phase was washed with water (100 ml), saturated brine (100 ml), and dried (MgSO₄). The solvent was removed under reduced pressure to give
30 6-chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid (20.3 g, 57%) as a light orange solid, mp 135-152°C.

Analytical sample recrystallized from aqueous MeOH, mp 180-210° (dec).

N⁶-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-
2',3'-di-o-isopropylidene-5'-uronic acid

5 A solution of 6-chloropurine riboside-2',3'-di-o-isopropylidene-5'-uronic acid (3.41 g, 10 mmol), 2-(3,5-dimethoxyphenyl)-2-(methylphenyl)ethylamine (2.71 g, 10 mmol) and NEt₃ (3.03 g, 30 mmol) were refluxed in EtOH (100 ml) stirring under N₂ for 18 hours. The solvent was 10 removed under reduced pressure, and the residue was dissolved in NaOH solution (0.25 M, 50 ml), washed with EtOAc (2x25 ml), acidified with concentrated HCl, and then extracted with EtOAc (3x30 ml). The combined organic extracts were washed with water (2x25 ml), saturated brine (25 ml), and dried (MgSO₄). 15 The solvent was removed under reduced pressure to give N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (4.94 g, 82%) as a light yellow solid foam, mp 113-121°C.

N⁶-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-
5'-uronic acid

20 N⁶-(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (1.50 g, 2.6 mmol) was stirred in aqueous TFA (10 ml, 1:9) under N₂ at 25 0°C for 4 hours. The reaction mixture was quenched by pouring onto EtOAc (50 ml), and most of the TFA was washed out with NaOH solution (2.2 M, 50 ml) and NaH₂PO₄ solution (0.2 M, 50 ml). The organic phase was washed with saturated brine (50 ml), dried (MgSO₄), and the solution concentrated under reduced pressure before residual volatiles were azeotroped 30 three times with toluene. The residual solid foam was dissolved in EtOH (24 ml) and triturated with ether to give N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronic acid (0.71 g, 51%) as a white powder, mp 129-139°C.

-42-

EXAMPLE 33

N^6 -(2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-
5'-uronamide

Dicyclohexylcarbodiimide (0.55 g, 2.7 mmol) was added to a suspension of 1-hydroxybenzotriazole (0.32 g, 2.4 mmol) in CH₂Cl₂ (20 ml) containing N^6 -(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (Example 32, 1.15 g, 2 mmol) stirred under N₂ at 0°. After 10 minutes NH₃ was bubbled through the mixture for 15 minutes at 0°C, and then the mixture was allowed to warm up to 25°C. It was then vacuum filtered, the residue rinsed with CH₂Cl₂ (10 ml) and the solvent removed from the combined filtrates under reduced pressure. The residual glassy solid was dissolved in aqueous TFA (10 ml, 1:9) and stirred under N₂ at 0°C for 2.5 hours. The reaction mixture was poured onto NaOH solution (125 ml, 1 M) and was extracted with EtOAc (100 ml). The organic layer was washed with water (50 ml), saturated brine (50 ml), and dried (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica (150 g) eluting with 5% MeOH in CHCl₃ to give N^6 -(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide (0.71 g, 61%) as a white crystalline solid, mp 181-184°C.

EXAMPLE 34

N^5 '-Methyl- N^6 -(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide

Triethylamine (0.61 g, 6 mmol) and methylamine hydrochloride (0.27 g, 4 mmol) were added sequentially 1 minute apart to a suspension of N-methyl-2-fluoropyridinium tosylate (0.42 g, 1.5 mmol) and N^6 -(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (Example 32, 0.58 g, 1 mmol) in CH₂Cl₂ (5 ml) stirred under N₂ at 0°C. After 1 hour the reaction mixture was diluted with EtOAc (25 ml) and washed with dilute HCl (1 M, 10 ml), water (10 ml), saturated brine (10 ml), and dried (MgSO₄). The

solvent was removed under reduced pressure, and the residual solid foam was dissolved in aqueous TFA (5 ml, 1:9 at 0°C) and stirred under N₂ for 2 hours. The reaction was quenched by addition of EtOAc (50 ml), and washing with NaOH solution (1 M, 50 ml) dilute Na₂CO₃ solution (50 ml), and saturated brine (25 ml), and drying (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (silica) eluting with 10% MeOH in CHCl₃ to give N^{5'}-methyl-N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide (0.36 g, 64%) as a white glassy foam, mp 122-127°C.

EXAMPLE 35

N^{5'}-Ethyl-N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide

Dicyclohexylcarbodiimide (0.52 g, 2.5 mmol) was added to a suspension of 1-hydroxybenzotriazole (0.27 g, 2 mmol) in CH₂Cl₂ (20 ml) containing N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-2',3'-di-o-isopropylidene-5'-uronic acid (Example 32, 1.15 g, 2 mmol) stirred under N₂ at 0°C. After 10 minutes ethylamine (0.27 ml, 4 mmol) was added. After 16 hours the reaction mixture was filtered, and the residue was rinsed with CH₂Cl₂ (10 ml). The solvent was removed from the combined filtrates under reduced pressure and the residual light yellow solid foam was dissolved in aqueous TFA (10 ml, 1:9) at 0°C and stirred under N₂ for 75 minutes. The reaction mixture was quenched with EtOAc (100 ml) and washed with NaOH solution (1 M, 100 ml), saturated Na₂CO₃ solution (50 ml), saturated brine (50 ml), and dried (MgSO₄). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (100 g) eluting with 5% MeOH in CHCl₃ to give N^{5'}-ethyl-N⁶-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide (0.86 g, 72%) contaminated with ≈10 mol% dicyclohexylurea, as a pale yellow solid foam, mp 103-112°C.

- 44 -

EXAMPLE 36

$\text{N}^5\text{-Cyclopropyl-N}^6\text{-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)}$
ethyl)adenosine-5'-uronamide

Triethylamine (0.20 g, 2 mmol) and cyclopropylamine (0.11 g, 2 mmol) were added sequentially 2 minutes apart to a mixture of N-methyl-2-fluoropyridinium tosylate (0.42 g, 1.5 mmol) and $\text{N}^6\text{-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)}$
ethyl)adenosine-2',3'-di- o -isopropylidene-5'-uronamic acid (Example 32, 0.58 g, 1.0 mmol) stirred in CH_2Cl_2 (5 ml) under N_2 at 25°C. After 15 minutes the reaction mixture was diluted with EtOAc (25 ml), and washed with dilute HCl (0.5 M, 10 ml), water (10 ml), saturated brine (10 ml), and dried (MgSO_4). The solvent was removed under reduced pressure and the residual solid foam was stirred in aqueous TFA (5 ml, 1:9) under N_2 at 0°C for 2 hours. The reaction mixture was quenched with EtOAc (50 ml), and washed with NaOH solution (1 M, 50 ml), dilute Na_2CO_3 solution (50 ml), saturated brine (25 ml), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by preparative TLC, eluting with 10% MeOH in CH_2Cl_2 , to give $\text{N}^5\text{-cyclopropyl-N}^6\text{-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)}$
ethyl)adenosine-5'-uronamide (0.39 g, 67%) as a white glass, mp 117-126°C.

EXAMPLE 37

$\text{N}^5\text{-Ethyl-N}^6\text{(-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)}$
ethyl)adenosine-5'-uronamide

N -Ethyl-6-chloropurine-ribofuranuronamide-2',3'-di- o -isopropylidene

Triethylamine (1.01 g, 10 mmol) was added to a suspension of 6-chloropurine ribofuranuronic acid-2',3'-di- o -isopropylidene (1.70 g, prepared in Example 32) and N-methyl-2-fluoropyridinium tosylate (2.12 g, 7.5 mmol) stirred in CH_2Cl_2 (25 mL) under N_2 at 0°C. After 15 minutes ethylamine (1 mL, ~15 mmol) was added. After a further 1 hour the reaction mixture was poured onto dilute HCl, (1N, 25 mL), the layers

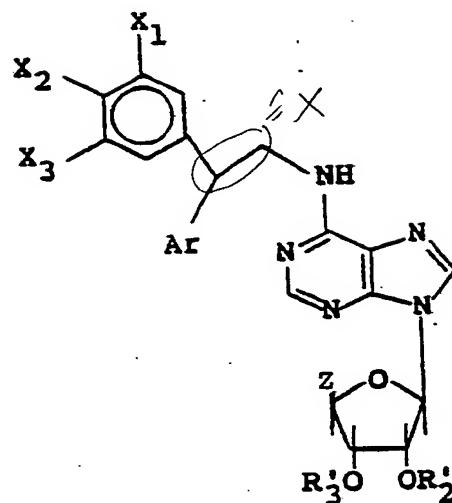
separated, and the aqueous layer extracted with CH_2Cl_2 (25 mL). The combined organic phases were washed with water (25 mL), saturated brine (25 mL), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was purified by 5 flash chromatography on silica gel, eluting with hexane/EtOAc to give N-ethyl-6-chloropurine-ribofuranuronamide-2',3'-di-o-isopropylidene (1.20 g, 65%) as an offwhite solid foam; mp 73-80°C.

10 N^{5'}-Ethyl-N⁶-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5'-uronamide
 (--2-(3,5-Dimethoxyphenyl)-2-(2-methylphenyl)ethylamine (0.17 g, 0.6 mmol, prepared as in Example 29),
 N-ethyl-6-chloropurine-ribofuranuronamide-2',3'-di-o-isopropylidene (0.22 g, 0.6 mmol) and triethylamine (0.12 g, 1.2 mmol) were refluxed in EtOH (6 mL) under N_2 for 20 hours.
15 The volatiles were removed under reduced pressure and the residual glass was stirred in aqueous TFA (1:9, 5 mL) under N_2 at 0°C for 2 hours. The mixture was diluted with EtOAc (50 mL) and washed with dilute NaOH (1M, 50 mL), dilute Na_2CO_3 solution (50 mL), saturated brine (50 mL), and dried (MgSO_4). The solvent was removed under reduced pressure, and the residue was 20 purified by preparative tlc (10% MeOH in CHCl_3 , rf 0.28) to give N^{5'}-ethyl-N⁶-((-)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine-5-uronamide (0.28 g, 83%) as a 25 white glass; mp 110-120°C.

-46-

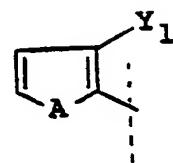
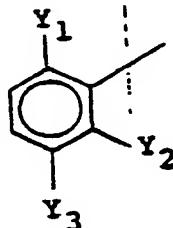
CLAIMS

1. A compound of the formula

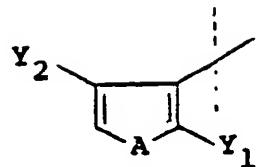


or a pharmaceutically acceptable acid addition salt thereof; wherein Ar is

5



or



wherein A is oxygen or sulfur and wherein X_1 , X_2 , X_3 , Y_1 , Y_2 and Y_3 may be independently selected from hydrogen, halogen, lower alkyl, lower alkylthio or alkoxy, and X_1 , X_2 , X_3 may also be trifluoromethyl with the proviso that Y_2 or Y_3 must be hydrogen and Y_2 and Y_3 taken together are $-(CH)_4$ with the further overall proviso that at least two of X_1 , X_2 , X_3 , Y_1 , Y_2 and Y_3 are not hydrogen.

R_2' and R_3' are each independently hydrogen, alkanoyl having two to twelve carbon atoms in a straight or branched alkyl chain which may be substituted by amino, benzoyl or benzoyl substituted by lower alkyl, lower alkoxy, halogen or trifluoromethyl; additionally, R_2' and R_3' may be linked together to form either a five-membered alkylidene ring having a total of up to twenty carbons such as, for example, isopropylidene, or a cyclic phosphate diester and R_5' may be a phosphate, hydrogen or dihydrogen phosphate, or an alkali metal or ammonium or dialkali or diammonium salt thereof; and

Z is $-(CH_2)_2-Q$ wherein Q is selected from the group consisting of hydrogen, hydroxy, halogen, cyano, azido, amino, lower alkoxy, lower acyloxy, lower thioalkyl, lower sulfonylalkyl,

$-P(=Y)(OR'')_2$, $-P(=Y)(OR'')(OR''')$ and taken together with R^3 is

-48-



wherein Y is oxygen or sulfur and R'' and R''' are independently hydrogen or lower alkyl; or (2)

TC
||
J

5 wherein J is O, S, NR₇ wherein R₇ is hydrogen, lower alkyl or cycloalkyl of from 3 to 7 carbons such as cyclopropyl, cyclobutyl, cyclopentyl and the like or 1- or 2-methylcyclopropyl, 1-, or 2-ethylcyclobutyl and the like; and

10 T is (a) NR₄R₅ wherein R₄ is straight chain lower alkyl having 1-4 carbon atoms; hydroxy, lower alkoxy or halogen substituted straight chain lower alkyl having 1-4 carbon atoms; cyclopropyl; secondary alkyl having 3-6 carbon atoms; hydroxy, lower alkoxy or halogen substituted secondary alkyl having 3-6 carbon atoms; alkenyl having 3 to 6 carbon atoms; aralkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the aryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups; and heteroarylalkyl having 1 to 4 carbons in the alkyl chain and optionally substituted in the heteroaryl nucleus with hydroxy, halogen, lower alkoxy or lower alkyl groups, and

15

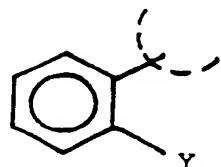
20

R₅ is hydrogen or straight chain lower alkyl having 1 to 4 carbons; or

25 (b) OR₄ wherein R₄ is as defined above.

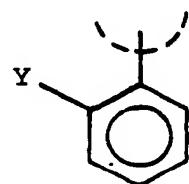
2. A compound of Claim 1 wherein Z is $-(CH_2)-Q$ wherein Q is OH.

3. A compound of Claim 2 wherein R_2' and R_3' are OH, and Ar is



wherein Z is as defined above, Y is Y_1 as defined above
5 when Y_1 is not hydrogen.

4. A compound of Claim 2 wherein X_1 , X_2 , wherein Ar is



wherein Y is as defined above, and Z is $-C(O)N(H)C_2H_4$.

5. A compound of Claim 1 and being N,6-(2-(2,6-dimethylphenyl)-2-phenethyl)adenosine.

6. A compound of Claim 1 and being N,6-(2-(2,6-dimethylphenyl)-2-(4-methylphenyl)ethyl)adenosine.

7. A compound of Claim 1 and being N,6-(2-(3,5-dimethylphenyl)-2-phenethyl)adenosine.

8. A compound of Claim 1 and being N,6-(2-naphth-1-yl-2-phenethyl)adenosine.

9. A compound of Claim 1 and being N,6-(2-(3,5-dichlorophenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine.

-50-

10. A compound of Claim 1 and being N,6-(2-(2,6-dichlorophenyl)-2-(phenethyl)adenosine.
11. A compound of Claim 1 and being N,6-(2-(3,5-dichlorophenyl)-2-phenethyl)adenosine.
12. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(3,5-dichlorophenyl)ethyl)adenosine.
13. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(2,6-dichlorophenyl)ethyl)adenosine.
14. A compound of Claim 1 and being N,6-(2-(3-chlorophenyl)-2-(3,5-dimethoxyphenyl)ethyl)adenosine.
15. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-phenethyl)adenosine.
16. A compound of Claim 1 and being N,6-(2-(2,5-dimethoxyphenyl)-2-phenethyl)adenosine.
17. A compound of Claim 1 and being N,6-(2-(2,6-dimethoxyphenyl)-2-phenethyl)adenosine.
18. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine.
19. A compound of Claim 1 and being N,6-(2-(3,4-dimethoxyphenyl)-2-phenethyl)adenosine.
20. A compound of Claim 1 and being N,6-(2-(3,5-diethoxyphenyl)-2-phenethyl)adenosine.
21. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-thien-2-yl)ethyl)adenosine.

22. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-naphth-1-yethyl)adenosine.
23. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.
24. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2,6-dimethylphenyl)ethyl)adenosine.
25. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(3-methoxyphenyl)ethyl)adenosine.
26. A compound of Claim 1 and being N,6-(2-(3,4,5-trimethoxyphenyl)-2-phenethyl)adenosine.
27. A compound of Claim 1 and being N,6-(2-(3,5-dimethoxyphenyl)-2-(2-methoxyphenyl)ethyl)adenosine.
28. A compound of Claim 1 and being N,6-(2-(3,4,5-trimethoxyphenyl)-2-(methylphenyl)ethyl)adenosine.
29. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl)adenosine.
30. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3-trifluoromethylphenyl)ethyl)adenosine.
31. A compound of Claim 1 and being N,6-(2-(2-methoxyphenyl)-2-(3,5-bis(trifluoromethyl)phenyl)ethyl)adenosine.
32. A compound of Claim 1 and being N⁶-((--)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.
33. A compound of Claim 1 and being N⁶-((+)-2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl)adenosine.

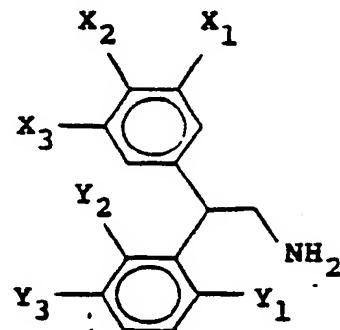
-52-

34. A compound of Claim 1 and being \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine.$
35. A compound of Claim 1 and being \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-5'\text{-uronide}.$
36. A compound of Claim 1 and being \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-5'\text{-uronamide}.$
37. A compound of Claim 1 and being \underline{N}^5' -methyl- \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-$
 $5'\text{-uronamide}.$
38. A compound of Claim 1 and being \underline{N}^5' -ethyl- \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-$
 $5'\text{-uronamide}.$
39. A compound of Claim 1 and being \underline{N}^5' -cyclopropyl- \underline{N}^6 -
 $(2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-5'\text{-uronamide}.$
40. A compound of Claim 1 and being $\underline{N},6$ -
 $(2-(3,5\text{-bis(trifluoromethyl)phenyl})-2\text{-phenethyl})adenosine.$
41. A compound of Claim 1 and being \underline{N}^5' -ethyl- \underline{N}^6 -
 $((-)-2-(3,5\text{-dimethoxyphenyl})-2-(2\text{-methylphenyl})ethyl)adenosine-5'\text{-uronamide}.$
42. A pharmaceutical composition for treating psychoses, pain,
angina or congestive heart failure comprising an
antipsychoses, analgesic, antianginal or anticongestive
heart failure effective amount of a compound of Claim 1
and a pharmacologically acceptable carrier.
- 5
43. A method of treating psychoses in mammals suffering
therefrom comprising administering to said mammals a
compound of Claim 1 in unit dosage form.

NM
JW RS

-53-

44. A method of treating pain in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.
45. A method of treating angina in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.
46. A method of treating congestive heart failure in mammals suffering therefrom comprising administering to said mammals a compound of Claim 1 in unit dosage form.
47. A process for preparing a compound of Claim 1 which comprises coupling a compound of the formula



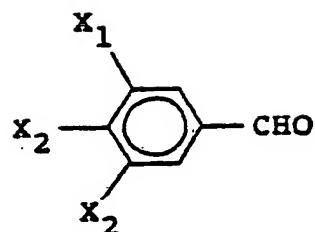
II

5

with 6-chloropurine riboside in the presence of triethyleneamine to obtain the compound of Claim 1.

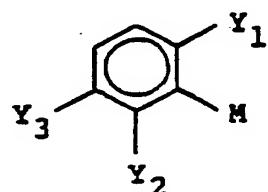
48. A process for the preparation of a compound of Claim 1 which comprises A) treating a compound of the formula

-54-



5

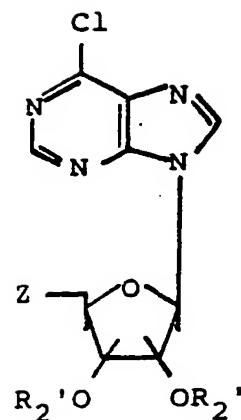
wherein x_1 , x_2 and x_3 are as defined above; with 1) CH_3NO_2 in the presence of NaOH and 2) $\text{CH}_3\text{SO}_2\text{Cl}$ in the presence of triethylamine; B) treating the product of A) with a compound of the formula



10

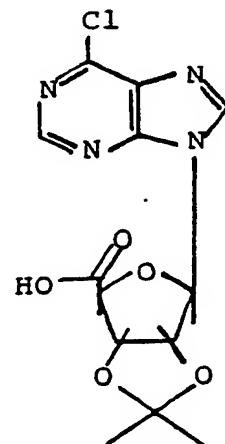
wherein y_1 , y_2 and y_3 are as defined above, and M is a Grignard or lithium moiety; in an aprotic solvent; then C) reducing the product of B) by treating with LiAlH_4 and finally D) coupling the product of C) with 6-chloropurine riboside of the formula

-55-



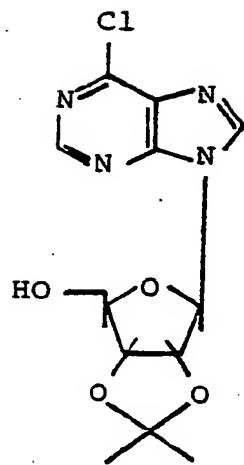
wherein Z is as defined above in the presence of triethylamine to obtain the compound of Claim 1.

49. A method for preparing a compound of the formula



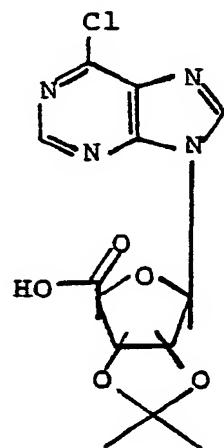
which comprises treating a compound of the formula

-56-

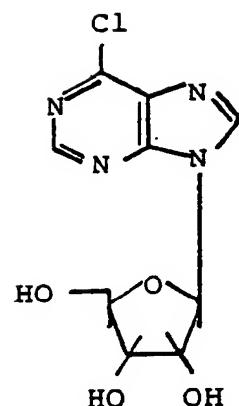


with H_2CrO_4 in acetone.

50. A process for the preparation of the compound of the formula



which comprises (1) treating a compound of the formula



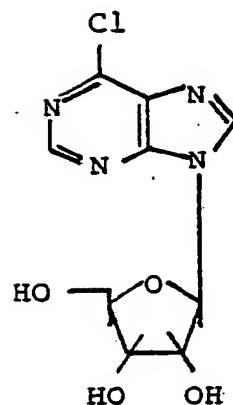
with ethyl orthoformate and tosic acid in acetone; and then (2) treating the product of step (1) with H_2CrO_4 in acetone.

51. A process for the preparation of a compound of Claim 1 wherein Z is



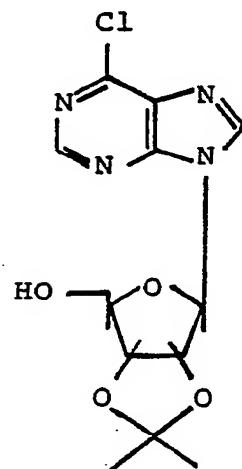
5 wherein J is O and T is NR_4R_5 when R_4 and R_5 are as defined above which comprises
(1) reacting a compound of the formula

-58-



X

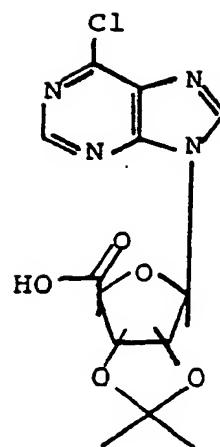
with ethyl formate and tosic acid in acetone; to obtain the compound of the formula



XI

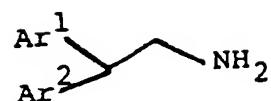
5 (2) treating the compound of the formula XI of step (1) with H_2CrO_4 in acetone; to obtain the compound of the formula

-59-



XII

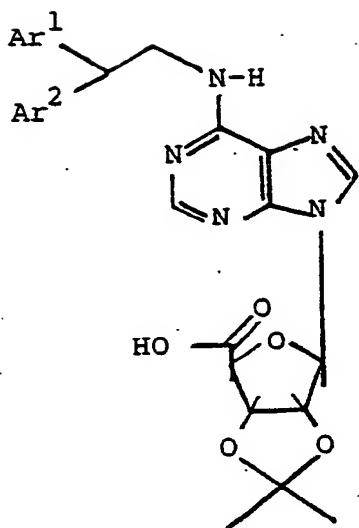
then (3)(a) treating the compound of the formula XII
of step (2) with



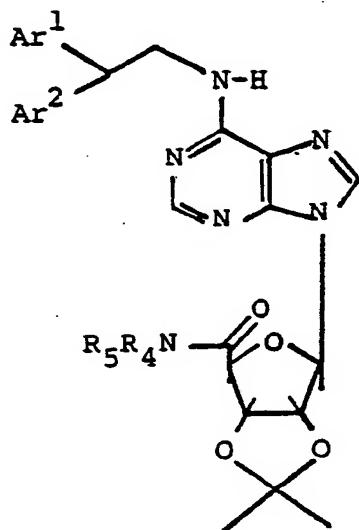
5

wherein Ar¹ and Ar² are as defined above in the presence
of triethylamine; to obtain the compound of formula

-60-



and then treating the compound of formula XIII with HNR_4R_5 in the presence of a coupling agent, to obtain



5

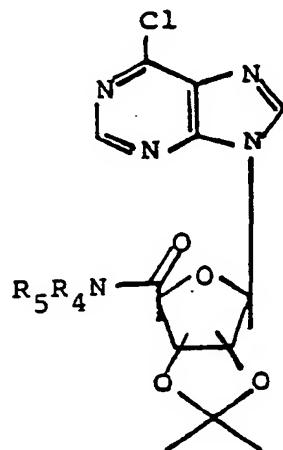
and alternatively further treating the compound of the formula XIV to obtain the compound of formula I wherein Z is

-61-

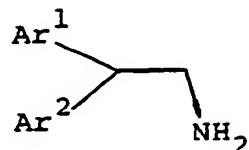


wherein J is O and T is NR_4R_5 wherein R_4 and R_5 are as defined above and R_2' and R_3' are other than propylidene; or

5 then (3)(b) treating the compound of formula XII of step (2) with HNR_4R_5 to obtain the compound of formula



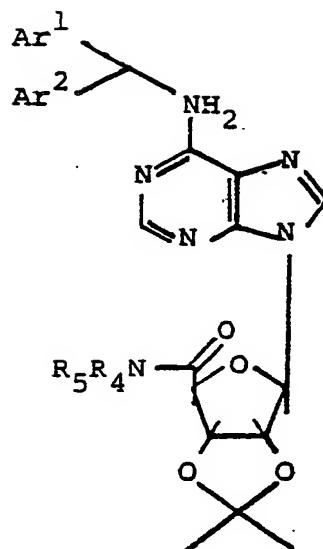
and then treating the compound of formula XVI with



10

to obtain the compound of the formula

-62-



XIV

and alternatively, further teaching the compound of the formula XIV to obtain the compound of formula I wherein Z is



5

wherein J is O and T is NR₄R₅ wherein R₄ and R₅ are as defined above and R_{2'} and R_{3'} are other than propylidene.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 87/02719

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁴

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: C 07 H 19/167; A 61 K 31/70

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System	Classification Symbols
IPC ⁴	C 07 H 19/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸	

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP, A, 0181129 (WARNER-LAMBERT CO.) 14 May 1986 see examples 1,6 --	1,42
Y	EP, A, 0152944 (BOEHRINGER MANNHEIM GmbH) 28 August 1985 see the whole document --	1,42
Y	EP, A, 0139358 (WARNER-LAMBERT CO.) 2 May 1985 --	1,42
A	US, A, 3781273 (BOEHRINGER MANNHEIM GmbH) 25 December 1973 see the whole document --	1,42
A	FR, A, 2195434 (BOEHRINGER MANNHEIM GmbH) 8 March 1974 see the whole document -----	1,42
*		

- Special categories of cited documents: ¹⁰
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

15th February 1988

International Searching Authority

EUROPEAN PATENT OFFICE

Date of Mailing of this International Search Report

11 APR 1988

Signature of Authorized Officer

M. VAN MOL

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 8702719
SA 19648**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 23/03/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0181129	14-05-86	AU-A- 4888885 JP-A- 61148194		08-05-86 05-07-86
EP-A- 0152944	28-08-85	DE-A- 3406533 JP-A- 60193998 US-A- 4704381		29-08-85 02-10-85 03-11-87
EP-A- 0139358	02-05-85	AU-A- 3078284 JP-A- 60075494 EP-A- 0251339 US-A- 4657897 US-A- 4657898		07-02-85 27-04-85 07-01-88 14-04-87 14-04-87
US-A- 3781273	25-12-73	NL-A- 7102026 FR-A, B 2081524 DE-A- 2007273 GB-A- 1279946 CH-A- 549596 CH-A- 549600 CA-A- 953714 AT-A, B 306251 AT-A, B 313483		20-08-71 03-12-71 26-08-71 28-06-72 31-05-74 31-05-74 27-08-74 15-02-73 15-01-74
FR-A- 2195434	08-03-74	NL-A- 7310870 DE-A- 2238923 GB-A- 1384518 AT-B- 325784 AU-A- 5885773 CH-A- 579587 AU-B- 470398 CA-A- 1003411 JP-A- 49045095 SE-B- 400086		12-02-74 14-02-74 19-02-75 10-11-75 06-02-75 15-09-76 11-03-76 11-01-77 27-04-74 13-03-78

App. No. 10/608,689
Filed: June 27, 2003
Inventor: BIGOT, et al.
Docket No. DEAV2002/0059 US NP
PRIOR ART